# Post Approval Study Plan for the S-ICD® System

Revision B
March 12, 2012

S-ICD® System, Consisting of:
Model 1010, SQ-RX™ Pulse Generator
Model 3010, Q-TRAK™ Subcutaneous Electrode
Model 4010, Q-GUIDE™ Electrode Insertion Tools
Model 2020, Q-TECH™ Programmer

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# Introduction

This post approval study plan for the S-ICD System incorporates the relevant elements as outlined in the following FDA Guidance Documents:

1. Guidance for Industry and FDA Staff: Procedures for Handling Post-Approval Studies Imposed by PMA Order. Issued: June 15, 2009
2. Draft Guidance for Industry and FDA Staff: Procedures for Handling Section 522 Postmarket Surveillance Studies. Issued: August 16, 2011

# Background

The benefit of transvenous ICD systems in primary and secondary prevention patient populations is supported by a number of large, prospective, randomized clinical trials. In spite of the overall success of transvenous ICD therapy, the post operative complications associated with the therapy have come under increased scrutiny in light of several highly publicized device recalls in recent years.

The S-ICD provides clinicians and patients with a viable therapeutic alternative to current transvenous ICDs. The S-ICD System IDE Clinical Investigation was the first study to demonstrate the safety and effectiveness of the S-ICD System in patients with Class I and II ICD indications. A post-approval study of the S-ICD System is proposed to confirm the continued safety of S-ICD System through 60 months.

## Study Purpose

The primary purpose of the proposed post-approval study is to demonstrate the 36-month S-ICD System complication-free rate, with continued follow-up and annual reporting through 60 months. While the S-ICD System IDE clinical investigation met its co-primary safety and effectiveness clinical endpoints, the post-approval study is intended to demonstrate the continued safety of the S-ICD System in a commercial clinical setting.

## Study Population

All patients implanted with an S-ICD System who provide written informed consent will be included in the study.

# Study Design

The S-ICD System post approval study will be an observational registry consisting of patients initially implanted with an S-ICD System in the premarket (IDE) clinical study and an additional prospectively enrolled cohort from approximately 50 US clinical centers. Cameron Health believes the proposed post approval study can be conducted in collaboration with the ACC NCDR® ICD Registry™.

All active US patients currently implanted with an S-ICD System (approximately 300 IDE patients, plus any implanted in a potential continued access IDE) will be approached to participate in the post-approval study to leverage their existing implant and follow-up experience. In addition, a new cohort of approximately 470 patients will be enrolled in the

post-approval study, resulting in an overall sample size of 800 patients. This sample size is designed to sufficiently power the primary endpoint analysis.

All patients enrolled in the post approval study will be followed for five years.

All complications associated with the S-ICD System will be tracked for all patients. Data will be collected to evaluate perioperative (≤ 30 days post implant), 180 day (6 months) and annual complication-free rates for the S-ICD System annually through five years of follow-up. An S-ICD System complication will be defined according to the same definitions used in the IDE study (caused by the S-ICD System and requiring an invasive corrective action).

These data will represent the first available long-term complication-free rate data for the S-ICD System and will serve to establish a benchmark for subcutaneous ICDs.

## NCDR ICD Registry

The NCDR ICD Registry is a CMS-mandated registry for hospitals that perform ICD implant procedures. The registry was selected as the sole repository for ICD implantation data for Medicare beneficiaries on April 1, 2006. The registry is currently collecting data from 1,489 hospitals in the US and has data from over 550,000 implants to date. The registry is accruing ICD implants at the rate of 10,000 per month with 79% of implants in the registry being performed in hospitals that enter all data on patients regardless of device indication or patient age. Thus, currently 90% of all ICD implants performed in the US are entered into the registry. In April 2010, the registry expanded to include the surveillance of lead performance and to include pediatric ICD implantations.

The scale of the registry makes it a powerful benchmarking tool for the evaluation of real world experience with the S-ICD System for de-novo implants and replacements as well as providing critical insight into the complication rates over time for this technology. An additional benefit of conducting the post approval study in collaboration with the NCDR ICD Registry is it may also allow additional comparisons of the complication-free rates for the S-ICD System with single and dual chamber ICD systems that use transvenous leads.

The following data is collected in the NCDR ICD Registry V2.1:

- Patient demographics
- Patient history and risk factors
- Device type (CRT-D, ICD)
- Procedure related adverse events

The NCDR ICD Registry collects baseline patient demographics and procedure related adverse events only. This limitation precludes a complete comparison with the IDE study results; however, the data from the registry combined with other resources (Social Security Death Index) will provide data to address the long-term mortality profile of the S-ICD patients. Although 79% of hospitals enter all patients in the registry, regardless of device indication and patient age, participation for non-Medicare beneficiaries is voluntary and the data collected is not monitored. The registry does use an audit program and publishes quality reports for audited sites. In addition, Cameron Health will use an active monitoring program for all clinical centers participating in the post approval study.

In summary, Cameron Health believes that a post approval study design as proposed would enable collaboration with the NCDR ICD Registry. Other post approval study designs may not be compatible with the NCDR ICD Registry.

## Methods

Study data will be collected and entered into the NCDR ICD Registry and analyzed at pre-determined intervals identified in the final post approval study protocol. Endpoint analyses and other observational analyses will be based on data provided by NCDR.

## Study Endpoints

A 36-month complication-free rate will be evaluated to assess the long-term safety of the S-ICD System. The endpoint will be evaluated against a performance goal that will be determined by adjusting the 6-month threshold established in the S-ICD System IDE clinical study (79%) downward to account for additional expected events between 6-36 months.

### Endpoint Hypotheses:

$H_o$: The 36-month complication-free rate of the S-ICD System ($p_1$) does not exceed the performance goal ($p_0$).

$$H_o: p_0 - p_1 > 0$$

$H_a$: The 36-month complication-free rate of the S-ICD System ($p_1$) meets or exceeds the performance goal ($p_0$).

$$H_a: p_0 - p_1 \leq 0$$

Where: $p_0$ is the 36-month performance goal, based on adjusting the 79% 6-month threshold downward to account for additional expected events between 6-36 months, and
$p_1$ is the actual 36-month complication-free rate of the S-ICD System for patients enrolled prospectively in the post-approval study

The definition of an S-ICD System complication will replicate the definition used in the S-ICD Clinical Investigation (IDE Study).

### Sample Size

The endpoint will be evaluated using a Kaplan-Meier estimate of the 36-month complication-free rate and a confidence interval based on the Peto estimate of the standard error (see for example Chernick and Friis, 2003[1]). The sample size of the prospective cohort will be sized to provide 80% power for statistically demonstrating that the safety performance of the S-ICD System exceeds the performance goal, assuming a complication-free rate consistent with the existing data for the S-ICD System and a significance level (α) of 0.05 (two-sided, equivalent to 0.025 one-sided).

[1] Chernick, M. R. and Friis, R. H. (2003) *Introductory Biostatistics for Health Sciences: Modern Applications Including Bootstrap*. Wiley, New York, page 343 Display 15.2

The sample size for the primary safety endpoint will be calculated as follows:

Let S be the Kaplan-Meier point estimate of the one year complication-free rate. The Peto formula for the 95% two-sided confidence interval for the complication-free rate is:

{S-1.96 √W, S+1.96 √W}, where W is the Peto estimate of the variance of S. $W = S^2 (1-S)/Nr$, where Nr is the number of patients remaining at risk for a first complication at one year.

Conditional on the value for Nr, the expected number of patients enrolled N would be Nr/S. So in terms of N, we can consider W to be S(1-S)/N. Values for N and S were determined such that the probability that [S-1.96 √W ≥ 0.79] is 0.80.

Based on the attrition rate in the IDE (approximately 10% at one year), Cameron Health believes an attrition rate of 20% over three years for the newly enrolled S-ICD patients is appropriate. Thus, an additional number of patients will be enrolled to account for expected attrition over the 36 month period.

## Non-Endpoint Evaluations

### Long Term Safety: Comparisons between IDE and Post Approval Cohorts

The 6 month – 5 year complication-free rate data for the new post approval cohort will be compared with the initial IDE cohort.

### Long Term Safety: Comparison to Transvenous ICDs in Matched Population

Collaboration with the NCDR ICD Registry may enable observational comparisons with transvenous ICD complications.

### Long Term Safety: Five-year Mortality Estimate

In addition, the post approval study will provide a means to collect additional mortality data in patients implanted with an S-ICD System over the five year follow-up period.

### Long Term Efficacy: First Shock and Episode Conversion Efficacy

First shock and and episode conversion efficacy will be calculated through the collection of spontaneous episode reports throughout the study period.

### Subgroup Analysis by Gender

In conformance with FDA's *Draft Guidance for Industry and Food and Drug Administration Staff - Evaluation of Sex Differences in Medical Device Clinical Studies,*[2] subgroup analyzes will be performed for each endpoint and non-endpoint evaluation by gender.

[2] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm283453.htm#6

## Monitoring

Participating sites will be monitored at least annually to verify source data, examine medical records for events, determine vital status and assess study participation status (to reduce losses to follow-up).

## Timelines

- Study initiation will begin within 3 months post PMA approval
- The number of sites with IRB approvals per month is estimated to be approximately 10 per month for 5 months.
- Estimated first enrollment is 4 months post PMA approval
- The number of enrollments per month is estimated at 30-50, once all sites are approved to enroll.
- The estimated date to complete enrollment is 18 months after the first enrollment.
- The estimated date to complete follow-up is 60 months after enrollment is complete
- The Final Study Report will be submitted no later than 3 months after last participant completes follow-up

## Reporting

Interim progress reports will be generated every 6 months for the first two years of the study and annually thereafter from the negotiated start date for the study. Reports will include sections outlined in the relevant FDA guidance documents pertaining to post approval studies.